Bioorganic & Medicinal Chemistry Letters 22 (2012) 1969–1975

Contents lists available at SciVerse ScienceDirect

Bioorganic & Medicinal Chemistry Letters

journal homepage: www.elsevier.com/locate/bmcl

SAR-study on a new class of imidazo[1,2-*a*]pyridine-based inhibitors of 5-lipoxygenase

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ARTICLE INFO

Article history:
Received 29 November 2011
Revised 11 January 2012
Accepted 12 January 2012
Available online 24 January 2012

Keywords:
Inflammation
5-Lipoxygenase
One-pot multicomponent reaction
Arachidonic acid cascade
Allergic diseases

ABSTRACT

A novel class of 5-lipoxygenase (5-LO) inhibitors characterized by a central imidazo[1,2-*a*]pyridine scaffold, a cyclohexyl moiety and an aromatic system, is presented. This scaffold was identified in a virtual screening study and exhibits promising inhibitory potential on the 5-LO. Here, we investigate the structure–activity relationships of this compound class. With *N*-cyclohexyl-6-methyl-2-(4-morpholinophenyl)imidazo[1,2-*a*]pyridine-3-amine (**14**), we identified a potent 5-LO inhibitor (IC_{50} = 0.16 μM (intact cells) and 0.1 μM (cell-free)), which may possess potential as an effective lead compound intervening with inflammatory diseases and certain types of cancer.

Eicosanoids are signaling lipids derived from polyunsaturated fatty acids which act as important regulators in immunity and inflammation.[1] Furthermore, diseases like rheumatoid arthritis, asthma, atherosclerosis and cancer are influenced by a subgroup of eicosanoids, the leukotrienes (LTs).[2–4] For LT biosynthesis, arachidonic acid (AA) is released from membrane phospholipids by phospholipase (PL) A_2 and transferred via the 5-lipoxygenase-activating protein (FLAP) to 5-lipoxygenase (5-LO).[5,6] 5-LO is a non-heme iron-containing enzyme and catalyzes the oxygenation of AA to 5(*S*)-hydroperoxy-6-*trans*-8,11,14-*cis*-eicosatetraenoic acid (5-HPETE). In the following, 5-HPETE gets reduced to the corresponding alcohol 5-HETE.[7] Alternatively, 5-HPETE can be dehydrated, which leads to the unstable epoxide LTA_4. LTA_4 itself is afterwards converted by LTA_4 hydrolase to LTB_4 which is a chemotactic and chemokinetic agent as well as an activator for phagocytes.[8] Furthermore, LTA_4 can be conjugated with reduced glutathione by LTC_4 synthase. The cysteinyl-containing LTs C_4, D_4 and E_4 cause bronchoconstriction and vascular permeability.[1] LTs also play a prominent role in chronic inflammation and in regulation of the adaptive immune response.[7] Though also anti-inflammatory properties of the 5-LO have recently been shown as the enzyme is involved in the biosynthesis of the resolvins, agents that trigger mechanisms of natural resolution of inflammation,[9] there are, based on the multiple pathophysiological actions of LTs, increasing therapeutic indications for 5-LO inhibitors including inflammation, allergic rhinitis, cardiovascular diseases, cancer and osteoporosis.[4,10] 5-LO as a drug target has been validated in many in vitro and in vivo studies[4] and 5-LO inhibitors are actively in clinical development. To date, the only 5-LO inhibitor that entered the market is A-64077 (zileuton),[11] which inhibits 5-LO by chelating its active site iron.[12] However, it exhibits some drawbacks, that is, the initial need to take it several times daily and the risk of hepatotoxicity.[13] Furthermore, given that many 5-LO inhibitory drug candidates lack sufficient selectivity or show mechanism-based side effects,[14–17] there is a strong need for novel 5-LO inhibitors.

Herein, we present the synthesis and SAR (structure–activity relationship) studies of a novel series of 5-LO inhibitors based on a central imidazo[1,2-*a*]pyridine scaffold (Fig. 1). Previously, we were able to identify 5-LO inhibitors containing this scaffold by ligand-based virtual screening.[18] Thereby, seven imidazo[1,2-*a*]pyridine based structures showed potent 5-LO inhibition (IC_{50} ~1 μM). Among those, compounds **1** and **2** revealed the most promising profile for inhibition of the 5-LO pathway in intact polymorphonuclear leukocytes (PMNL; IC_{50} = 0.9 and 0.6 μM, respectively (Fig. 1)) and were therefore selected as structural templates of this study.

Abbreviations: 5-H(P)ETE, 5(*S*)-hydro(pero)xy-6-*trans*-8,11,14-*cis*-eicosatetraenoic acid; 5-LO, 5-lipoxygenase; AA, arachidonic acid; FLAP, 5-lipoxygenase-activating protein; LT, leukotriene; PL, phospholipase; PMNL, polymorphonuclear leucocytes; SAR, structure–activity relationship; S100, 100,000*g* supernatant.

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doi:10.1016/j.bmcl.2012.01.038

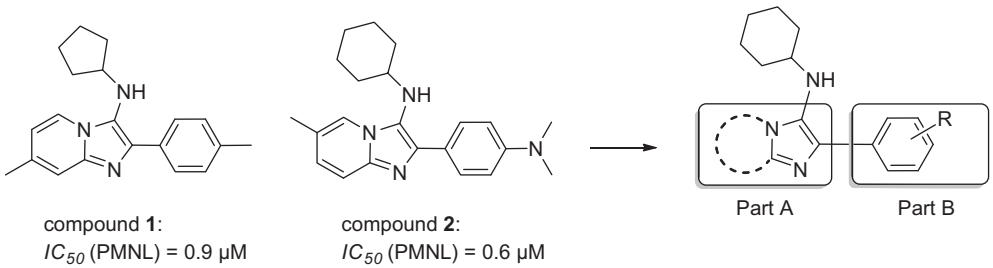
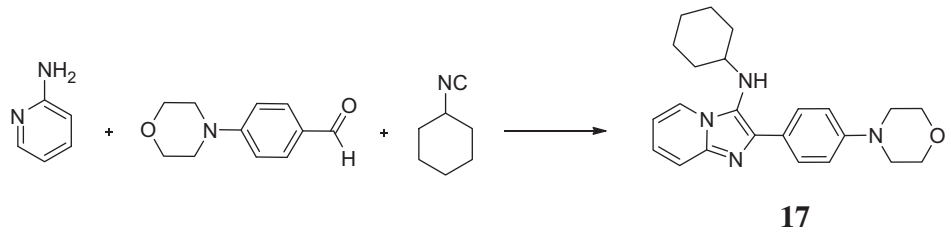
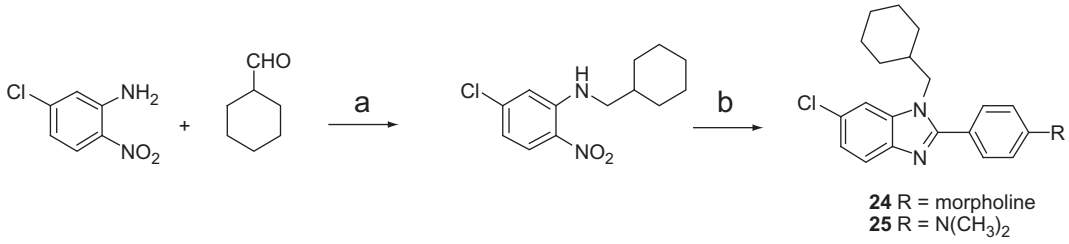


Figure 1. Lead compounds **1** and **2**[18]; general structure of presented compounds.



Scheme 1. Synthesis of the imidazo[1,2-*a*]pyridine derivatives, exemplified at compound **17**. Reagents and conditions: acetic acid (99%), MeOH; rt, overnight.



Scheme 2. Synthesis of benzimidazole derivatives **24** and **25**. Reagents and conditions: (a) nitroaniline, glacial acetic acid, $NaBH(OAc)_3$, DCE, rt, overnight. (b) N,N-substituted *p*-amino benzaldehyde, $Na_2S_2O_4$, EtOH/DMSO, 80 °C, 48 h.

The synthesis of compounds **5**, **14–23** and **26–31** follows a multicomponent procedure as outlined in Scheme 1.[19] The whole structure series was prepared by means of these multicomponent reactions, which are an excellent source for novel bioactive compounds.[20] Especially the isocyanide-based reactions have proven to provide drug-like compounds with high diversity and optimization potential. In brief, the respective benzaldehyde and aminopyridine (or structural analogs) were dissolved together in absolute methanol (MeOH). Next, cyclohexyl isonitrile and glacial acetic acid were added to the solution. Overnight stirring resulted in precipitation of the product. Purification was subsequently done by recrystallization from ethanol/ethyl acetate (EtOAc).

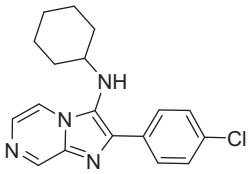
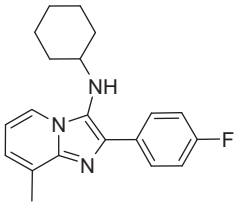
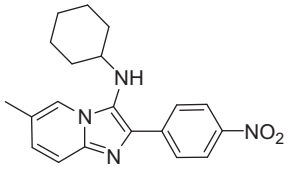
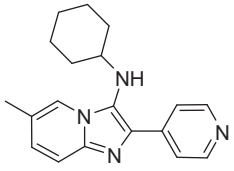
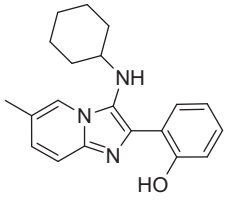
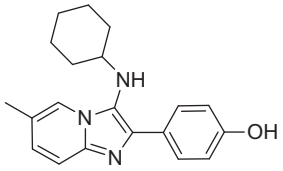
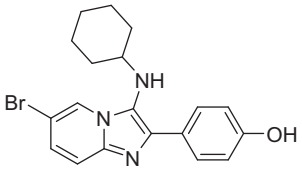
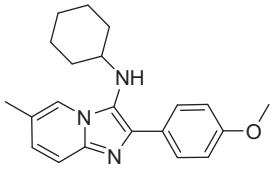
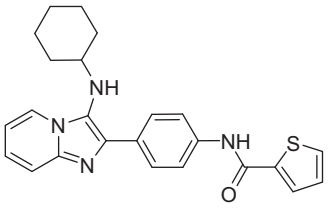
Benzimidazole derivatives **24** and **25** were synthesized as outlined in Scheme 2 within a modified two-step procedure described by Yang et al.[21] Briefly, 3-chloro-5-nitro-aniline reacted with cyclohexanecarboxaldehyde in a reductive amination as described by Abdel-Magid et al.[22] In the following step, a reductive cyclization with the corresponding aldehyde in presence of sodium dithionite ($Na_2S_2O_4$) was carried out. Compounds **24** and **25** were purified by recrystallization from ethanol.

The characterization of all compounds for their 5-LO inhibitory activity was carried out in intact polymorphonuclear leukocytes (PMNL) as well as in a cell-free system (S100). The PMNL assay provides cellular conditions and is useful to assess membrane permeation properties of the compounds. The latter assay (S100) was chosen to distinguish between direct inhibition of 5-LO (comparable inhibition in both assays) and indirect effects like FLAP or $cPLA_2$ interaction (lower inhibitory activity in the cell-free assay).[23] Please consider that the discussion is focused on the IC_{50} values of the PMNL assay to regard intracellular bioavailability. However, almost all compounds were equally active in both assays, indicating direct 5-LO inhibitory effects and overall, the potencies measured by both methods correlate well for most of the compounds. Outliers that diverged from this correlation (cf. correlation-plot, Supplementary data Figure S5) are discussed in each case. Detailed information about the assay conditions and dose-response curves of all tested compounds are provided as Supplementary data. BWA4C,[24] another well-established iron-ligand type 5-LO inhibitor, was used as control reference compound in both assays (IC_{50} values of 0.05 μM (PMNL S100) and 0.08 μM (intact PMNL) (Table 1), which is similar to the literature[24]).

In order to investigate the underlying SAR and to optimize the structure of compounds **1** and **2** with respect to 5-LO inhibition, we investigated the influence of different substituents at the central imidazo[1,2-*a*]pyridine core (part A) and the additional aromatic center (part B, see Fig. 1) on inhibition of 5-LO product formation. The cyclohexyl amino moiety was kept constant within the complete SAR study, due to the fact that this group has previously turned out as relevant feature for the potency of 5-LO inhibition.[18]

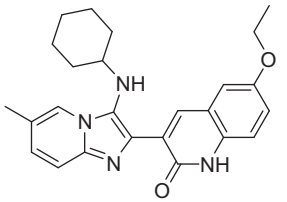
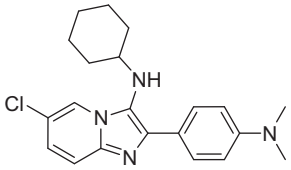
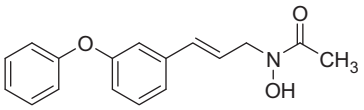
In the first part of our study, we performed a preliminary screening of commercially available compounds exhibiting the imidazo[1,2-*a*]pyridine core of the Asinex database (www.asinex.com, Moscow, Russia) (Table 1). Among those, compound **3** with

Table 1
Inhibition of 5-LO product formation (in intact PMNL and cell-free S100) by test compounds from the preliminary screening[a]

Compound	Structure	5-LO product formation IC_{50} (μM)	
		PMNL	S100
3*		2.3	21.5
4*		2.1	1.2
5		1.53	>30
6*		7.2	7.7
7*		1.9	1.8
8*		2.0	0.6
9*		1.1	0.9
10*		1.3	0.5
11*		0.4	0.4

(*continued on next page*)

Table 1 (*continued*)

Compound	Structure	5-LO product formation IC_{50} (μM)	
		PMNL	S100
12*		1.8	21.6
13*		0.1	0.08
BWA4C		0.08	0.05

[a] The asterisk (*) indicates commercially available compounds purchased from Asinex.

an imidazo[1,2-*a*]pyrazine scaffold and an electron withdrawing *para*-chloro group in part B showed a decreased inhibitory activity of 5-LO product formation (IC_{50} = 2.3 μM) compared to compounds **1** and **2**.

The other compounds **4–13** showed broad structural variations in part B and rather marginal modifications at the central imidazo[1,2-*a*]pyridine core (part A). Within those, compound **4** features a methyl-substituted (position 8) imidazo[1,2-*a*]pyridine scaffold and a *para*-fluoro residue at part B. This compound exhibited the same decreased inhibitory potential as compound **3** (IC_{50} = 2.1 μM).

Six compounds of this screening kept a methyl group at position 6 in part A with different substituents in part B (**5**–**8**, **10**, **12**). Introduction of *para*-nitro (**5**), -hydroxyl (**8**) or -methoxy (**10**) in part B resulted in IC_{50} values of 1.53, 2.0 and 1.3 μM, respectively. The hydroxyl group in *ortho* position (**7**) did not alter the inhibitory activity (IC_{50} = 1.9 μM) at all. On the contrary, introduction of *para*-hydroxy in part B combined with a bromo moiety in part A (position 6) (**9**) resulted in a marginal higher potency (IC_{50} = 1.1 μM). Furthermore, the replacement of the phenyl moiety in part B by an unsubstituted pyridine (**6**) turned out to be even less effective (IC_{50} = 7.2 μM) but the replacement with a bulky substituent (**12**) did not alter the inhibitory potency (IC_{50} = 1.8 μM) in intact cells.

The introduction of a bulky substituent in *para*-position at part B (**11**) finally led to a potent inhibition of 5-LO product formation (IC_{50} = 0.4 μM). The most potent compound from this screening was found in **13** which displays structural similarity to the previously identified compound **2**, containing a *para*-dimethylamino group in part B. The introduction of a chloro moiety in part A (position 6) resulted in a six-fold higher potency in inhibiting 5-LO product formation (IC_{50} = 0.1 μM).

In summary, all compounds of the preliminary screening were able to inhibit 5-LO product formation at least at low micromolar ranges. The highest potency was achieved by introduction of a *para*-dimethylamino substitution in compound **13** or by the introduction of an additional bulky moiety in part B (**11**).

Considering the inhibitory activity in the cell-free S100 assay, most compounds showed a similar potency compared to the cellular assay. This led us to the conclusion that our presented compounds directly interact with 5-LO. Interestingly, three compounds **3**, **5** and **12** were dramatically less active in the cell-free assay (IC_{50} >20 μM) compared to intact cells. Compound **3** with the imidazo[1,2-*a*]pyrazine scaffold approved the importance of the imidazo[1,2-*a*]pyridine scaffold for direct 5-LO binding. Further the nitro group (**5**) or the bulky substituent of compound **12** in part B seems to disturb the binding to the 5-LO protein. The potent inhibitory activity in intact PMNL might be an indicator for indirect inhibition of 5-LO product formation possibly by an interaction with FLAP or $cPLA_2$, which has to be elucidated.

For systematic investigation of the SAR, we used a synthetic strategy based on the one-pot procedure described by Groebke et al.[19] Thereby, the most potent compounds **2** and **13** served as structural templates. Within this part of the study, we focused on the investigation of the substitution in position 6 (part A) as well as the amino group at the backbone (Table 2). As additional computational binding studies gave us a hint for the binding mode of these compounds,[25] we designed derivatives expected to provide shielding of the bound inhibitor from the solvent by extending the dimethylamino moiety in part B of compound **2** to a morpholine group. The yielded compound **14** (IC_{50} = 0.16 μM) showed a three-fold higher potency compared to compound **2** supporting our binding mode hypothesis for this compound pair.[25] Consequently, we next synthesized compound **15** combining the substituents of compound **14** (morpholine moiety in part B) and **13** (chloro residue in part A). The activity of **15** was comparable to compound **13** and **14** (IC_{50} = 0.17 μM). The replacement of chloro- by a slightly bigger bromo-moiety in compound **16** did not alter activity (IC_{50} = 0.15 μM). Removal of the halogen in this position (**17**) led only to a slightly decreased potency (IC_{50} = 0.42 μM) compared to compound **14**. Due to the promising inhibitory activity of these morpholine derivatives, we molecular pharmacologically characterized the inhibitory mode of action of the most potent representative, compound **14**, in a second study.[25] This compound shows direct, allosteric and selective inhibition of 5-LO.[25] It has distinct properties from the three known classes of 5-LO inhibitors (iron-ligand type, redox type, and non-redox type inhibitors[12]) and lacks several characteristic drawbacks known for the class of nonredox type 5-LO inhibitors: The inhibitory efficacy of compound **14** is neither influenced by the redox tone in the cell or the concentration of exogenous AA nor by the stimulus for 5-LO activation, factors crucial for the efficacy of 5-LO inhibitors in vivo.[26,27] These findings encouraged us to further investigate this scaffold class.

Table 2
Influence of imidazo[1,2-*a*]pyridine substituents on inhibition of 5-LO product formation

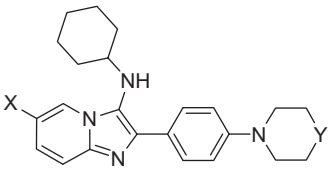
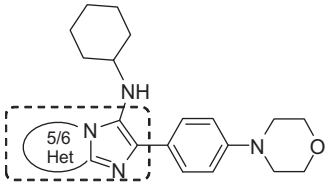
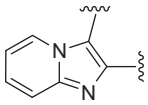
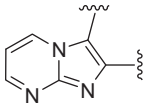
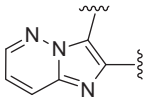
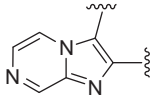
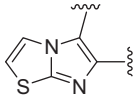
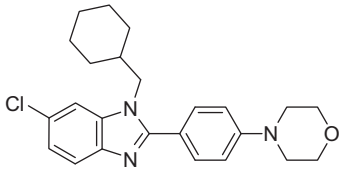
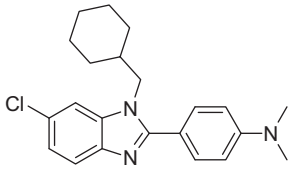
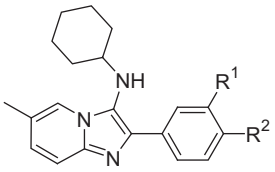
Compound				
			5-LO product formation IC_{50} (μM)	
	X	Y	PMNL	S100
14	CH_3	O	0.16	0.1
15	Cl	O	0.17	0.27
16	Br	O	0.15	0.77
17	H	O	0.42	0.51
18	Cl	CH_2	0.14	0.06
19	Cl	*N*-Boc	0.47	0.06

Table 3
Influence of heterocyclic core replacement on inhibition of 5-LO product formation

Compound		5-LO product formation IC_{50} (μM)	
		PMNL	S100
17		0.42	0.51
20		3.55	6.10
21		1.76	2.22
22		1.8	2.62
23		1.50	0.61
24		1.2	5.8
25		0.5	>10

To complete the sub-series based on compound **14**, we kept the chloro-residue at position 6 constant and replaced the morpholine-ring by a piperidine moiety (**18**). This resulted in a marginal increased potency (IC_{50} = 0.14 μM). In contrast, the introduction

Table 4
Influence of lipophilic backbone optimization on inhibition of 5-LO product formation

Compound			5-LO product formation IC_{50} (μM)	
	R^1	R^2	PMNL	S100
26	OMe	H	1.22	0.43
27	OMe	OMe	1.3	0.72
28	OPh	H	0.5	0.05
29	H	OBn	0.28	0.03
30	H	OPh	0.26	0.08
31	OBn	H	0.43	0.04

of *N*-Boc-piperazine instead of the morpholine-ring (**19**) caused a slight loss of activity (IC_{50} = 0.47 μM). Due to synthetic difficulties we were not able to obtain the deprotected derivative.

All tested derivatives of this sub-series were able to inhibit 5-LO product formation in submicromolar ranges, although it remains to be elucidated if these compounds show the same promising characteristics as compound **14**.

Based on the potent morpholine moiety in part A, we focused on the central imidazo[1,2-*a*]pyridine part and synthesized different bicyclic scaffolds in part A (Table 3). Therefore, we introduced an additional nitrogen resulting in imidazo[1,2-*a*]-pyrimidine (**20**), -pyridazine (**21**), -pyrazine (**22**) and -thiazole (**23**) fused scaffolds, respectively. In summary, introduction of any additional nitrogen to the bicyclic scaffold led to at least four- to eight-fold decreased activity (IC_{50} = 1.5–3.5 μM) compared to the imidazo[1,2-*a*]pyridine scaffold in **17** (IC_{50} = 0.42 μM) corroborating the promising inhibitory potential of the morpholine derivatives.

Furthermore, two benzimidazole derivatives (**24**, **25**) were synthesized as analogs to compounds **13** and **15** which showed a two- to seven-fold decrease of inhibitory activity (IC_{50} = 0.5 and 1.2 μM). Interestingly, both benzimidazole derivatives just weakly inhibited 5-LO product formation in the cell-free assay (IC_{50} >10 and 5.8 μM). Therefore we conclude that additional, indirect effects contribute to its inhibition of 5-LO product formation in the cellular assay.[23] In summary, the initial imidazo[1,2-*a*]pyridine scaffold turned out to exhibit the most potent inhibition of 5-LO product formation. Additional introduction of a methyl- or chloro-residue in position 6 resulted in an increased inhibition of 5-LO product formation.

In order to complete the study of the SAR, we focused again on the lipophilic backbone based on the structure of compound **10** (Table 4)**.** Keeping the methyl group in position 6 (part A) constant, we prepared a set of compounds featuring different ether moieties instead of amines. Introduction of 3- (**26**) or 4-methoxy at part B (**10**) as well as 3,4-dimethoxy-phenyl moieties (**27**) resulted in low micromolar inhibition of 5-LO product formation (IC_{50} = 1.2–1.3 μM). Substitution by the bulkier 3- (**28**) or 4-phenoxy (**30**) as well as 3- (**31**) or 4-benzyloxy (**29**) moieties led to a submicromolar inhibitory activity. The introduction at position 4 resulted in a nearly two-fold higher potency (IC_{50} = 0.26 and 0.28 μM) than the introduction at position 3 (IC_{50} = 0.5 and 0.43 μM). The greater flexibility of the benzyloxy moieties does not seem to have influence on the inhibitory activity compared to the phenoxy substituents. These compounds also inhibit 5-LO product formation in submicromolar concentration ranges in the S100 assay (IC_{50} = 0.03–0.72 μM). The overall correlation between the cell-free and whole cell assay is rather high (R^2 = 0.68) for all tested compounds, however, several outliers could be identified (cf. correlation-plot, Supplementary data Figure S5): Compounds **19**, **28**, **29** and **31** exhibit significantly (p >0.95) higher potency in cell-free assay system than expected. While the Boc carbamate group of compound **19** might be cleaved in whole-cell system, compounds **28**, **29** and **31** might accumulate in cell membrane due to the high lipophilicity.

In summary, we have developed a set of potent 5-LO inhibitors characterized by a central imidazo[1,2-*a*]pyridine scaffold. Starting with a preliminary screening of commercially available substances, we investigated the SAR of broad structural modifications of the imidazo[1,2-*a*]pyridine compounds. Thereby, we were able to identify a series of 5-LO inhibitors which are active in submicromolar concentrations in intact cells and a cell-free system. Imidazo[1,2-*a*]pyridines and related scaffolds were synthetically accessible by means of multicomponent one-pot Groebke reaction. We prepared a set of potent direct 5-LO inhibitors by systematic variation of the heterocyclic core, the core substituents and the phenyl substituents. The most potent compounds show a five- to 10-fold higher inhibitory potency than zileuton (IC_{50} = 0.5–1 μM[11]). This together with the promising molecular pharmacological profile in mind (demonstrated with compound **14**[25]) encourages us for further investigations to develop novel effective anti-inflammatory drugs based on this imidazo[1,2-*a*]pyridine scaffold.

Acknowledgment

The authors thank LOEWE Lipid Signaling Forschungszentrum Frankfurt (LiFF), the Oncogenic Signaling Frankfurt (OSF), the EU (LSHM-CT-2004-0050333) and Fonds der Chemischen Industrie for financial support. E.B. thanks DAAD-La Caixa (Spain) for a fellowship.

Supplementary data

Supplementary data (synthetic conditions, ^1H and ^{13}C NMR-data of intermediates and final compounds, mass spectrometry and combustion analysis data of final compounds, assay systems) associated with this article can be found, in the online version, at doi:10.1016/j.bmcl.2012.01.038.

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